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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/569,583	GALLAGHER, NEIL	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,9,11 and 24-28* is/are pending in the application.

4a) Of the above claim(s) *24-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,9,11 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 17, 2008 has been entered. Claims 2, 9, 11, 24-28 are pending in this application. Claims 24-26 and 28 remain withdrawn from consideration as being drawn to nonelected species. Claims 2, 9, 11 and 27 are examined on the merits in this office action.

Maintained Rejection-35 U.S.C. 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 2, 9, 11 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janus et al (US 2002/0055457) in view of Curwen et al (Poster EORTC-NCI-AACR, 2002), Nelson et al (BJU International, 2000, 85 (Suppl 2), 45-48) and Walczak et al (Expert Opin. Investig. Drugs, 2002).

5. The instant claims are drawn to a combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl)phenyl)pyridine-3-sulfonamide and a bisphosphonate (pamidronic acid or a pharmaceutically acceptable salt thereof). The claims are additionally drawn to a pharmaceutical composition comprising a combination in association with a pharmaceutically acceptable diluent or carrier.

6. Janus et al disclose a method of inhibition of bone metastases including in cancer patients an effective amount of an endothelin ET-A receptor antagonist (see claim 1). The reference further teaches that the primary cancer is prostate cancer (see claim 4). Furthermore, the reference teaches that the method comprises administration of a therapeutic agent, bisphosphonate (see claim 9). The reference teaches that therapeutic agent (bisphosphonate) addition impedes net bone loss (see claim 8). Additionally, the reference teaches the pharmaceutical formulations, the compounds may be administered orally, buccally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles (see paragraph [0115] and [0117]). This reads on claims 1 and 11. The difference between the reference and the instant claims is that the reference does not teach N-(3-methoxy-5-methylpyrazin-2-yl)-2-)4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide.

7. However, Curwen et al teach that ZD4054 (N-(3-methoxy-5-methylpyrazin-2-yl)-2-)4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide), a specific endothelin A receptor antagonist has utility in prostate cancer and metastatic bone disease (see poster, Figure 1, Results and Discussions). The reference further teaches that in in vitro studies, ZD4054 is a high-affinity ligand for the human ET_A receptor, with a pIC_{50} value of 8.27, while ZD4054 had no measurable affinity for the ET_B receptor (see Results, In vitro radioligand binding studies). Additionally, the reference teaches that ZD4054 is a potent ETA receptor antagonist in vivo, producing a dose-related response (see Figure 2a and Results, Intravenous antagonist potency).

8. Nelson et al teach that the endothelin (ETs) are identical in all mammals and many higher vertebrates; the ET receptors are also very similar (see p. 45, left column, 2nd paragraph). Additionally, the reference teaches that every prostate cancer cell line tested produces ET-1 mRNA and protein (see p. 45, right column, 2nd paragraph). Furthermore, the reference teaches that using a selective ETA receptor antagonist, the abdominal constrictor response of mice to ET-1 was completely inhibited (see p. 46, right bottom paragraph and p. 47, top left paragraph).

9. Walczak et al teach that men with hormone-independent prostate cancer are at risk for skeletal morbidity (see p. 1742, 1st 2 lines of "4. Bone-targeted therapy"). The reference further teaches that bisphosphonates exert their action by inducing apoptosis of osteoclasts. Bisphosphonates have demonstrated in vitro inhibitory effect on breast and prostate cancer ell adhesion to bone, and a direct cellular effect in inhibiting tumor cell invasion and proteolytic activity of matrix metalloproteinases. Pamidronate disodium

and zolendronic acid have also shown in vitro inhibition of prostate cancer cell growth (see p. 1742, section 4.1).

10. Therefore, it would have been obvious to one of ordinary skill in the art to combine the bisphosphonate and endothelin receptor antagonist. There is a reasonable expectation of success, since bisphosphonate is used in treatment of prostate cancer and endothelin receptor antagonist (ZD4054) is used in the treatment of prostate cancer, thus combining the two into a combination compound would show at least an additive effect. Additionally, the ordinary skilled artisans would be motivated to combine the teachings of the prior arts because Curwen et al teach that ZD4054 is a high-affinity ligand for the human ET_A receptor, while ZD4054 ha no measurable affinity for the ET_B receptor. Furthermore, Janus et al teach that bisphosphonate addition impeded bone loss (see claim 8). Therefore, since ZD4054 is selective for ET_A receptor, one would expect it to be active.

Response to Applicant's Arguments

11. Applicant argues to the KSR analysis used in Examiner's response to Applicant's arguments on page 7 of the previous office action. Applicant argues that the according to KSR and the Guidelines, an invention should only be considered to be obvious when the combined elements give predictable results. Applicant argues that the Examiner has failed to establish even a prima facie argument that it would be obvious to combine ZD4054 with a bisphosphonate, since none of the references provide motivation to combine these two compounds. Applicant argues that "the presently claimed

combination surprisingly produces a far greater than additive effect." Applicant further submitted Williams et al., Eur. J. Cancer Supplement 2006; 4(12):15, and argues that "in this research, the effect of ZD4054 alone, pamidronate alone and a combination of ZD4054 and pamidronate on the formation of bone metastases in a mouse model are compared...combining ZD4054 with pamidronate resulted in the surprising and unexpected finding that the combination actually prevented any detectable bone metastases such that no bone metastases were detected for the duration of the study." Lastly, Applicant argues that correct test in KSR is that the claimed combination of elements must give a predictable results, for an invention to be considered obvious."

12. Applicant's arguments have been fully considered but have not been found persuasive because the prior arts combined is prima facie obvious of the instant application. Janus et al teach a method of inhibition of bone metastases by administering an effective amount of an endothelin ET-A receptor antagonist. Janus et al also teach that the method comprises administration of a therapeutic agent, bisphosphonate and this addition impedes net bone loss in treating prostate cancer. Curwen et al teach that ZD4054 is a specific endothelin A receptor antagonist and has utility in prostate cancer and metastatic bone disease. Nelson reference teaches that the endothelin (ETs) are identical in all mammals and many higher vertebrates, and the ET receptors are also very similar, and that every prostate cancer cell line tested produces ET-1 mRNA and protein. Walczak et al teach that bisphosphonates exert their action by inducing apoptosis of osteoclasts, and have demonstrated in vitro inhibitory effect on breast and prostate cancer cell adhesion to bone, and a direct cellular effect in

inhibiting tumor cell invasion and proteolytic activity of matrix metalloproteinases. Walczak reference further teaches that pamidronate disodium and zoledronic acid have shown in vitro inhibition of prostate cancer cell growth. Therefore, it would have been obvious to combine the teachings of the prior arts to produce a pharmaceutical composition comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-)4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide and bisphosphonate (pamidronate), since Janus et al show that ET-A receptor antagonist and bisphosphonate addition impedes net bone loss and is for treating prostate cancer, and other references show the activity of ET-A receptor antagonist against prostate cancer and metastatic bone disease. There is a reasonable expectation of success, since bisphosphonate is used in treatment of prostate cancer and endothelin receptor antagonist (ZD4054) is used in treatment of prostate cancer, therefore, combining the two into a combination compound would show at least an additive effect. Further, since ZD4054 is selective for ET-A receptor, and Janus et al disclose that bisphosphonate addition impedes bone loss, there is a reasonable expectation that the addition of the two compounds into one composition would have an additive effect.

In regards to Applicant's argument that there is no motivation provided in the prior arts to combine the compounds, the MPEP states the following: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kekhoven*, 626 F.2d 846, 850, 205 USPQ 1069,

1072 (CCPA 1980) (citation omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious). See also *In re Crockett*, 279 F.2d 274, 126, USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating case iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Ouadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). Therefore, one would be motivated to combine two known compounds each of which is taught by the prior art to be useful for the same purpose to form a third composition to be used for the very same purpose.

In regards to the KSR analysis, the Court stated that "when there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasps. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727,_,82 USPQ2d 1385, 1397 (2007). Bisphosphonate is used in treatment of prostate cancer and endothelin receptor antagonist (ZD4054) is used in treatment of prostate cancer, therefore, combining the two into a combination compound would show at least an additive effect. Applicants have argue that there is evidence to illustrate a greater than additive effect. However, Applicants have not

provided what one would expect from the combination prior to filing of the instant application and how the results observed are indeed unexpected. The MPEP also states "a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage" See MPEP 716.02 (a). It is the position of the rejection that the combination of elements gave a predictable results. Therefore, one of ordinary skill in the art would have been motivated to combine two known compounds for formation of a third compound for the treatment of same disease or disorder.

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thur, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654

/Anish Gupta/

Primary Examiner, Art Unit 1654